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Glycopyrronium/ Formoterol fumarate dihydrate

BEVESPI AEROSPHERE™
7.2 mcg/ 5.0 mcg per actuation
Pressurised Suspension for Inhalation

Anticholinergic/Selective β_2-Adrenergic Agonist

1. NAME OF THE MEDICINAL PRODUCT

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE), 7.2 micrograms/ 5.0 micrograms, pressurised inhalation, suspension

2. FORMULATION

Each delivered dose (the dose that leaves the mouthpiece) contains glycopyrronium bromide 9.0 micrograms, equivalent to 7.2 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5.0 micrograms, equivalent to 4.8 micrograms of formoterol fumarate. This corresponds to a metered dose of glycopyrronium bromide 10.4 micrograms, equivalent to 8.3 micrograms of glycopyrronium, and formoterol fumarate dihydrate 5.8 micrograms, equivalent to 5.6 micrograms of formoterol fumarate.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised suspension for inhalation

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Dosage and method of administration

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should be administered as two inhalations taken twice daily, in the morning and in the evening, by the orally inhaled route only. Patients should be advised not to take more than two inhalations twice daily.

Missed dose

If a dose is missed, it should be taken as soon as possible and the next dose should be taken at the usual time. A double dose should not be taken to make up for a forgotten dose.

Special patient populations

Renal impairment
No dosage adjustment is necessary for patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Elderly patients
No dosage adjustment is necessary for elderly patients (see section 5.2).

Children and adolescents
There is no relevant use of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in children and adolescents (under 18 years of age) in the indication of COPD.

Method of administration

For inhalation use.

For detailed instructions, refer to the Instructions for use, handling and disposal**.** Patients should be instructed how to administer the product correctly and advised to read the instructions for use carefully.

The inhaler can be used with the Aerochamber Plus® spacer device. This may be useful for patients who find it difficult to synchronise breathing in with inhaler actuation.

4.3 Contraindications

Hypersensitivity to the active substances or any of the excipients.

4.4 Special warnings and special precautions for use

Asthma

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should not be used to treat asthma. Clinical studies of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in asthma have not been conducted.

Paradoxical bronchospasm

As with other inhaled medicines, administration of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) may cause paradoxical bronchospasm. If this occurs, treatment with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should be stopped and other treatments considered.

Not for acute use

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) is not indicated for the treatment of acute episodes of bronchospasm.

Cardiovascular effects

As for all β_2-agonists caution should be observed in patients with thyrotoxicosis and in patients with severe cardiovascular disorders, such as ischemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with long QTc-interval.

Systemic effects

In three clinical trials of 24-weeks and a 28-week safety extension study evaluating Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in subjects with COPD, there was no evidence of a treatment effect on potassium. Metabolic effects of hyperglycaemia and hypokalaemia may be observed with high doses of β_2-adrenergic agonists. The effects are usually transient and hypokalaemia does not require supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5).

Anticholinergic activity

Due to its anticholinergic activity, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should be used with caution in patients with symptomatic prostatic hyperplasia, urinary retention or with narrow-angle glaucoma.

Renal impairment

Formal pharmacokinetic studies using Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) have not been conducted in patients with renal impairment. As glycopyrronium is predominantly renally excreted, patients with severe renal impairment (creatinine clearance of < 30 mL/min) should be treated with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) only if the expected benefit outweighs the potential risk (see section 5.2).

Hepatic impairment

As formoterol is primarily eliminated via metabolism an increased exposure can be expected in patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE).

COPD medicinal products

Co-administration of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) with other anticholinergic and/or long-acting β_2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

Metabolic interactions

Formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations (see section 5.2). Glycopyrronium does not inhibit or induce CYP450 enzymes at therapeutically relevant concentrations (see section 5.2).

Drug-induced hypokalaemia

Possible initial hypokalaemia may be potentiated by concomitant medications, including non-potassium sparing diuretics.

β-adrenergic blockers

Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of formoterol.

Other pharmacodynamic interactions

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should be administered with caution to patients being treated with medicinal products known to prolong the QTc interval (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in pregnant women.

Single-dose studies in humans found that very small amounts of glycopyrronium passed the placental barrier. There are no adequate data from use of formoterol in pregnant women. In animal studies, formoterol and glycopyrronium, individually, have caused adverse effects in reproduction studies at very high doses/systemic exposure levels (see section 5.3).

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding

It is not known whether glycopyrronium or formoterol are excreted in human milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

Studies in rats have shown slight reductions in fertility only at dose levels higher than the maximum human exposure to formoterol (see section 5.3). It is unlikely that Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) administered at the recommended dose will affect fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on the pharmacological profile, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

As Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) contains glycopyrronium and formoterol, the type and severity of adverse reactions associated with each of the components may be expected with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE).

The safety evaluation of the pivotal program for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) included 5,450 subjects with COPD in three 24-week lung function trials, and one long-term safety extension study of 28 weeks. A total of 1,588 subjects received at least 1 dose of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in the pivotal studies.

Tabulated summary of adverse reactions

The tabulated list of adverse reactions is based on the experience with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in clinical trials and post-approval experience with the individual components and related products.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 1 Adverse drug reactions by frequency and system organ class (SOC)

Frequency	**SOC**	**MedDRA term**
Common ≥1% to <10%	*Psychiatric disorders*	Anxiety
	Nervous system disorders	Headache
		Dizziness
	Gastrointestinal disorders	Dry mouth
		Nausea
	Renal and urinary disorders	Urinary tract infection
	Musculoskeletal and connective tissue disorders	Muscle spasms
	General disorders and administration site conditions	Chest pain

Uncommon ≥0·1% to <1%		
	Metabolism and nutrition disorders	Hyperglycaemia
	Psychiatric disorders	Agitation, restlessness, insomnia
	Cardiac disorders	Tachycardia, palpitations Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles)
	Nervous system disorders	Tremor
	Immune system disorders	Hypersensitivity
	Renal and urinary disorders	Urinary retention

4.9 Overdose

There is limited evidence on the management of overdose with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE). An overdose of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) may lead to exaggerated anticholinergic and/or β_2-adrenergic signs and symptoms; the most frequent of which include blurred vision, dry mouth, nausea, muscle spasm, tremor, headache, palpitations and systolic hypertension.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) contains two bronchodilators: glycopyrronium is a long-acting muscarinic antagonist (anticholinergic) and formoterol is a long-acting β_2-adrenergic agonist. The combination of these substances with different mechanisms of action results in additive efficacy compared to using either component alone. As a consequence of the differential density of muscarinic receptors and β_2-adrenoceptors in the central and peripheral airways of the lung, muscarinic antagonists are more effective in relaxing central airways and β_2-adrenergic agonists are more effective in relaxing peripheral airways; relaxation of both central and peripheral airways with combination treatment may contribute to its beneficial effects on lung function.

Glycopyrronium is a long-acting muscarinic antagonist (anticholinergic) with a rapid onset of action. Bronchodilation is induced by inhibition of the M3 receptor.

Formoterol is a potent selective β2-adrenoceptor agonist. Bronchodilation is induced by causing direct relaxation of airway smooth muscle as a consequence of the increase in cyclic AMP through activation of adenylate cyclase.

Pharmacodynamic effects

In clinical studies, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) demonstrated statistically significant improvements in lung function, FEV_1, over 12 hours following administration, demonstrated by the primary endpoint (change from baseline in morning pre-dose trough FEV_1). Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) demonstrated an onset of action at 5 minutes after the first dose based on a mean increase in FEV_1 compared to placebo of 187 mL, 186 mL and 179 mL in TRIAL 1, 2 and 3 respectively. The onset of action of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) was comparable to that of formoterol fumarate. A robust bronchodilator effect (peak FEV_1) relative to baseline was evident from day one with numerically larger effects observed at subsequent evaluations over the 6-month treatment period.

Cardiac electrophysiology

No clinically relevant effects of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) on QT-interval compared with placebo were seen in a double-blind, single-dose, placebo- and positive-controlled (moxifloxacin) crossover QT trial in 69 healthy subjects.

No clinically significant effects of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) on cardiac rhythm were observed in two studies on 24-hour Holter monitoring in a total of 229 patients who received Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) twice daily.

Clinical efficacy and safety

The safety and efficacy of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) were evaluated in a clinical development program that included eight dose-ranging trials, a 2-week cardiovascular safety trial, a 4-week dose indicator trial, five supporting efficacy studies including two 4-week crossover studies to evaluate 24 hour lung function and three placebo-controlled lung function trials (TRIAL 1, TRIAL 2 and TRIAL 3) of 24-weeks duration, and included a 28-week extension of TRIALS 1 and 2, to evaluate safety over 1 year. The efficacy of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) is based on the dose ranging trials and the efficacy component of the 2-week cardiovascular safety trial in 1,059 subjects with COPD and the 3 placebo-controlled confirmatory trials in 5,433 subjects with COPD. TRIAL 1, TRIAL 2 and TRIAL 3

were 24-week, randomized, double-blind, placebo-controlled, parallel-group trials in subjects with moderate to very severe COPD. TRIAL 1 also included an open-label active control, tiotropium. Efficacy was measured by lung function, symptom outcomes, disease-specific health status, rescue medication use and COPD exacerbations.

In TRIALS 1 and 2, the first co-primary endpoint was the change from baseline in morning pre-dose trough FEV_1 over 24 weeks and the second co-primary end-point was the SAC TDI (Self-administered Computerised Transition Dyspnoea Index) focal score over 24 weeks. The secondary end-points were peak change from baseline in FEV_1 within 2 hours post-dosing, change from baseline in SGRQ total score, change from baseline in average daily rescue Ventolin HFA, and time to onset of action on Day 1.

In TRIAL 3, the primary endpoint was change from baseline in morning pre-dose trough FEV_1 over 24 weeks. The secondary endpoints were: interviewer-administered TDI focal score, peak change from baseline in FEV_1 within 2 hours post-dosing, change from baseline in SGRQ total score, change from baseline in average daily rescue Ventolin HFA use, and time to onset of action on Day 1.

Effects on lung function

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) twice daily provided statistically significant improvements in lung function (FEV_1) compared with placebo and its individual components (glycopyrronium [GP] and formoterol fumarate [FF]). In Phase III studies, onset of action was seen within 5 minutes of the first dose and effects were maintained over the dosing interval. There was a sustained effect over time in the six months and one year Phase III studies.

In TRIAL 1, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) showed statistically significant improvements in trough FEV_1 over 24 weeks relative to placebo, GP and FF of 158 mL, 60 mL and 64 mL respectively ($p<0.0001$). Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) also showed improvements in peak FEV_1 within 2 hours post-dose over 24 weeks relative to placebo, GP and FF of 288 mL, 123 mL and 81 mL respectively ($p<0.0001$).

In TRIAL 2, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) showed statistically significant improvements in trough FEV_1 over 24 weeks relative to placebo, GP and FF of 129 mL, 55 mL and 57 mL respectively ($p<0.0001$). Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) also showed statistically significant improvements in peak FEV_1 within 2 hours post-dose over 24 weeks relative to placebo, GP and FF of 278 mL, 129 mL and 76 mL respectively ($p<0.0001$).

In TRIAL 3, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) showed statistically significant improvements in trough FEV_1 over 24 weeks relative to

placebo, GP and FF of 155 mL, 55 mL and 72 mL respectively (p<0.0001). Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) also showed statistically significant improvements in peak FEV_1 within 2 hours post-dose over 24 weeks relative to placebo, GP and FF of 293 mL, 141 mL and 97 mL respectively (p<0.0001).

Additionally, two 4-week crossover studies were performed to evaluate 24 hour lung function (FEV_1) at Day 29 of treatment, compared to placebo, in a total of 123 patients with COPD. In the first study, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) showed statistically significant improvements (p<0.0001) compared to placebo in FEV_1 AUC_{0-24}, FEV_1 AUC_{0-12}, and FEV_1 AUC_{12-24} of 265 mL, 251 mL, and 277 mL, respectively. In the second study Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) showed statistically significant improvements (p<0.0001) compared to placebo of 249 mL, 255 mL, and 242 mL respectively.

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) also showed statistically significant improvements (p<0.0001) compared to placebo in post-dose morning and evening mean peak IC (Inspiratory Capacity), measured on Day 29 of 248 mL and 312 mL (first study) and 335 mL and 381 mL, respectively, (second study).

Symptom relief and disease-specific health status benefit

Breathlessness and other symptom outcomes

In TRIAL 3, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided a statistically significant improvement in breathlessness with an improvement in the TDI focal score over 24 weeks compared to placebo, of 0.80 units (p<0.0001). Improvements in the TDI focal score over 24 weeks compared to GP and FF were 0.33 units (p=0.0125) and 0.15 units (p=0.2530), respectively. In the symptomatic population, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided a statistically significant improvement in the TDI focal score over 24 weeks compared to placebo, of 0.73 units (p=0.0048). Improvements in the TDI focal score over 24 weeks compared to GP and FF were 0.41 units (p=0.0425) and 0.20 units (p=0.3379), respectively.

In TRIAL 3, the proportion of patients who responded with at least the minimum clinically important difference (MCID) of 1 unit TDI focal score over 24 weeks was greater for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) (57%) compared with placebo (37%) and each monotherapy component (47% for GP and 54% for FF), with odds ratios of 1.49 (95% CI 1.17, 1.91), 1.15 (95% CI 0.90, 1.47), and 2.25 (95% CI 1.64, 3.08), for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs GP, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs FF, and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs placebo, respectively.

In TRIAL 1, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided a statistically significant improvement in breathlessness with an improvement in the SAC TDI focal score over 24 weeks compared to placebo, of 0.47 units (p = 0.0003). Improvements in the SAC TDI focal score over 24 weeks compared to GP and FF were 0.27 units (p = 0.0086) and 0.16 units (p = 0.1060) respectively. In TRIAL 2, statistically significant improvements in the SAC TDI focal score over 24 weeks compared to placebo, GP and FF were 0.33 units (p=0.0041), 0.21 units (p = 0.0199) and 0.28 units (p = 0.0028), respectively.

Health-related quality of life

In TRIAL 3, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided a statistically significant improvement in disease-specific health-related quality of life, as indicated by a reduction in the St. George's Respiratory Questionnaire [SGRQ] total score over 24 weeks compared to placebo, of -3.50 units (p<0.0001). Improvements compared to GP and FF were -1.62 units (p=0.0165) and -0.27 units (p=0.6908), respectively.

In the symptomatic population (COPD assessment test ≥ 15 at baseline), Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided a statistically improvement compared to placebo, of -3.83 units (p<0.0068). Differences over 24 weeks compared to GP and FF were -2.99 units (p=0.0066) and 0.32 units (p=0.7787), respectively.

In TRIAL 1, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided improvements in the SGRQ total score over 24 weeks compared to placebo, GP and FF of -2.39 units (p=0.0053), -1.90 units (p = 0.0052) and -0.75 units (p = 0.2640), respectively.

In TRIAL 2, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) provided improvements in the SGRQ total score over 24 weeks compared to placebo, GP and FF of -1.66 units (p = 0.0534), -1.28 units (p = 0.0605) and -1.22 units (p = 0.0760) respectively.

In TRIAL 3, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) was 47%, 40%, 45%, and 34% for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE), GP, FF and placebo, respectively, with odds ratios of 1.34 (95% CI, 1.04, 1.74), 1.08 (95% CI 0.83, 1.39), and 1.73 (95% CI 1.25, 2.40), for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs GP, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs FF, and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs placebo, respectively.

In the symptomatic population, the SGRQ responder rate was 52%, 43%, 50%, and 38% for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE), GP, FF and placebo, respectively, with odds ratios of 1.44 (95% CI 1.00, 2.06), 1.06 (95% CI 0.74, 1.52),

and 1.75 (95% CI 1.11, 2.76), for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs GP, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs FF, and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs placebo, respectively.

In TRIAL 1, the SGRQ responder rate was 39%, 33%, 37%, and 31% for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE), GP, FF and placebo, respectively, with odds ratios of 1.27 (95% CI 0.97, 1.66), 1.07 (95% CI 0.82, 1.40), and 1.39 (95% CI 0.99, 1.97), for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs GP, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs FF, and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs placebo, respectively.

In TRIAL 2, the trends were similar with responder rates of 44%, 36%, 37% and 36% for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE), GP, FF and placebo respectively, and odds ratios of 1.37 (95% CI 1.05, 1.79), 1.33 (95% CI 1.02, 1.74), and 1.35 (95% CI 0.97, 1.88), for Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs GP, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs FF and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) vs. placebo, respectively.

COPD exacerbation reductions

Pooled data from the three 24-week pivotal trials showed Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) reduced the risk of moderate or severe COPD exacerbations compared with placebo (Hazard Ratio [HR] = 0.717 [p = 0.0012]), GP (HR = 0.816 [p = 0.0168]) and FF (HR = 0.852 [p = 0.062]), and Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) had a lower rate of moderate or severe COPD exacerbations compared with placebo (Rate Ratio [RR] = 0.74 [p = 0.0059]), GP (RR = 0.88 [p = 0.1491]) and FF (RR = 0.89 [p = 0.220]).

Use of rescue medication

In TRIAL 1, Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) reduced the use of rescue medication over 24 weeks compared to placebo, GP and FF by 1.08 ($p<0.0001$), 0.26 ($p = 0.0619$) and 0.01 ($p = 0.9683$) puffs per day, respectively. In TRIAL 2, reductions compared to placebo, GP and FF were 1.04 ($p<0.0001$), 0.57 ($p<0.0001$) and 0.29 ($p = 0.0274$) puffs per day. In TRIAL 3, reductions compared to placebo, GP and FF were 0.98 ($p<0.0001$), 0.77 ($p<0.0001$) and 0.41 ($p=0.0344$) puffs per day, in those using rescue medication at entry.

5.2 Pharmacokinetic properties

Absorption

Following inhalation of the glycopyrronium and formoterol combination, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately. For pharmacokinetic purposes each component can therefore be considered separately.

Glycopyrronium
Following inhaled administration of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in subjects with COPD, glycopyrronium C_{max} occurred at 5 minutes. Steady state is achieved within 2-3 days of repeated dosing of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) and the extent of exposure is approximately 2.3 times higher than after the first dose.

Formoterol
Following inhaled administration of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in subjects with COPD, formoterol C_{max} occurred within 20 to 60 minutes. Steady state is achieved within 2-3 days of repeated dosing with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) and the extent of exposure is approximately 1.5 times higher than after the first dose.

Lung deposition
A lung deposition study with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) conducted in healthy volunteers demonstrated that on average 38% of the nominal dose is deposited into the lung. Deposition was consistent with the width of the aerodynamic particle size distribution with both central and peripheral deposition observed.

Distribution

Glycopyrronium
The estimated glycopyrronium Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 741 L, and 2990 L, respectively, via population pharmacokinetic analysis. Over the concentration range of 2-500 nmol/L, plasma protein binding of glycopyrronium ranged from 43% to 54%.

Formoterol
The estimated formoterol Vc/F (volume of the central compartment), and Vp1/F (volume of the peripheral compartment) are 1030 L, and 647 L, respectively, via population pharmacokinetic analysis. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%.

Metabolism

Glycopyrronium
Based on literature, and an *in-vitro* human hepatocyte study, metabolism plays a minor role in the overall elimination of glycopyrronium. CYP2D6 was found to be the predominant enzyme involved in the metabolism of glycopyrronium.
In-vitro studies indicate the glycopyrronium does not inhibit any subtype of cytochrome P450 and that there is no induction of CYP1A2, 2B6, or 3A4 at therapeutically relevant concentrations.

Formoterol
The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation. *In-vitro* studies indicate that formoterol does not inhibit the CYP450 enzymes at therapeutically relevant concentrations.

Elimination

After IV administration of a 0.2 mg dose of radiolabeled glycopyrronium, 85% of the dose was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The terminal elimination half-life of glycopyrronium derived via population pharmacokinetics analysis was 15 hours.

The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the faeces. The terminal elimination half-life of formoterol derived via population pharmacokinetics analysis was 13 hours.

Linearity/non-linearity
Linear pharmacokinetics were observed for glycopyrronium (dose range: 14.4 to 115.2 mcg) and formoterol (dose range: 2.4 to 19.2 mcg) after oral inhalation.

Special patient populations

Age, gender, race/ethnicity and weight
A population pharmacokinetic analysis of glycopyrronium was performed based on data collected in a total of 311 subjects with COPD. The pharmacokinetics of glycopyrronium was best described by a two-compartment disposition model with first-order absorption and linear elimination. The typical clearance (CL/F) of glycopyrronium was 124 L/h.

A population pharmacokinetic analysis of formoterol was performed based on data collected in a total of 437 subjects with COPD. The pharmacokinetics of formoterol was best described by a two-compartment disposition model with a first-order rate constant of absorption and linear elimination. The typical clearance (CL/F) of formoterol was 99 L/h.

Dose adjustments are not necessary based on the effect of age, gender and weight on the pharmacokinetic parameters of glycopyrronium and formoterol.

There were no major differences in total systemic exposure (AUC) for both compounds between healthy Japanese and Western subjects. Insufficient pharmacokinetic data are available to compare exposure for other ethnicities or races.

Elderly patients
Based on available data, no adjustment of the dosage of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in geriatric patients is necessary.

The confirmatory trials of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal impairment
Studies evaluating the effect of renal impairment on the pharmacokinetics of glycopyrronium and formoterol were not conducted. The effect of renal impairment on the exposure to glycopyrronium and formoterol for up to 12 weeks was evaluated in a population pharmacokinetic analysis. Estimated glomerular filtration rate (eGFR) varied from 30 to 196 mL/min representing a range of moderate to no renal impairment. The systemic exposure (AUC_{0-12}) in subjects with COPD with moderate-severe renal impairment (eGFR of 30-45 mL/min) is approximately 30% higher for glycopyrronium compared to subjects with COPD with normal renal function (eGFR of >90 mL/min). Subjects with COPD with both low body weight and moderate-severe impaired renal function may have an approximate doubling of systemic exposure to glycopyrronium. Renal function was found not to affect exposure to formoterol.

Hepatic impairment
No pharmacokinetic studies have been performed with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) in patients with hepatic impairment. However, because formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment. Glycopyrronium is primarily cleared from the systemic circulation by renal excretion and hepatic impairment would therefore not be expected to lead to unsafe systemic exposure.

5.3 Preclinical safety data

Non-clinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicology.

The toxicity observed in animal studies with glycopyrronium and formoterol were associated with the pharmacological actions of formoterol in the dog, including effects mainly on the

cardiovascular system consisting of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of β-adrenoceptor agonists. No significant effects attributable to glycopyrronium were seen.

Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at high systemic exposure and implantation losses, as well as decreased early postnatal survival and birth weight at considerably higher systemic exposures than those reached during clinical use. However, these animal experimental results have little relevance to man. A slight increase in the incidence of uterine leiomyomas has been observed in rats and mice treated with formoterol; an effect which is considered to be a class-effect in rodents after long-term exposure to high doses of β_2-adrenoreceptor agonists.

Animal reproduction studies with glycopyrronium have shown reduced rat and rabbit fetal weights at approximately 2700 and 5400 times the MRHDID on a $\mu g/m^2$ basis, and low body weight gain of rat offspring before weaning was observed at 270 times the MRHDID. No evidence of carcinogenicity was seen in 2-year studies in rats and mice.

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) contains the excipients 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride as part of the spray-dried porous particle technology in the pressurized liquid propellant HFA-134a. The safe use of HFA-134a has been fully evaluated in preclinical studies. DSPC and calcium chloride have a long history of safe use in man and are approved excipients worldwide. Furthermore, inhaled toxicology studies carried out with Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) have shown no evidence of any toxicity attributable to the excipients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrofluoroalkane (HFA-134a)

Porous particles (comprised of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to the outer carton.

As packaged for sale – 2 years

After removal from the foil pouch – 3 months (120 actuation pack size)

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C.

6.5 Nature and contents of container

A pressurized metered dose inhaler, comprising an internally-coated aluminium canister, sealed with a metering valve, fitted with an attached dose indicator device and fitted into a white plastic actuator body with an orange dust cap. Each inhaler is individually packaged in a foil laminate pouch containing a desiccant sachet and packed into a carton.

6.6 Availability

Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) 7.2 mcg/ 5.0 mcg per actuation Pressurised Suspension for Inhalation – 1 inhaler x 120 actuations wrapped in foil pouch in box of 1's

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Read this Instruction for Use before you start using Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) and each time you get a new pack. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

See section 4.2. The canister should not be broken, punctured or burnt, even when apparently empty. Do not use or store near heat or open flames. Do not expose to temperatures above 50°C.

The actuator should be cleaned weekly for the first 3 weeks.

Important Information:

- **For oral inhalation use only**.
- Use Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) exactly as your doctor tells you to.
- If you have any questions about the use of your inhaler, ask your doctor or pharmacist.

Parts of your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler (See Figure 1):

- Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) comes as a canister that fits into an actuator with a dose indicator.
  - **Do not** use the Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) actuator with a canister of medicine from any other inhaler.
  - **Do not** use the Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) canister with an actuator from any other inhaler.

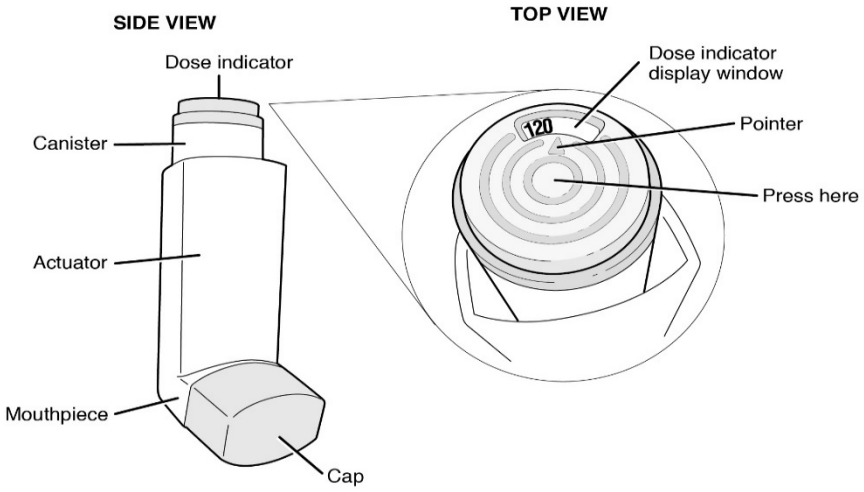

Figure 1

- Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) comes with a dose indicator located on the top of the canister (**See Figure 1**). The dose indicator display window will show you how many puffs of medicine you have left. A puff of medicine is released each time you press the centre of the dose indicator.

Before you use Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) for the first time make sure that the pointer on the dose indicator is pointing to the right of the "120" inhalation mark in the dose indicator display window (**See Figure 1**).

- The pointer will be pointing to 120 after 10 puffs are delivered from Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE). This means that there are 120 puffs of medicine left in the canister (**See Figure 2a**).
- The pointer will be pointing between 100 and 120 after you take 10 more puffs. This means that there are 110 puffs of medicine left in the canister (**See Figure 2b**).
- The pointer will be pointing to 100 after you take 10 more puffs. This means that there are 100 puffs of medicine left in the canister (**See Figure 2c)**.

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

- The dose indicator display window will continue to move after every 10 puffs. The number in the dose indicator display window will continue to change after every 20 puffs.

Figure 2d

- The colour in the dose indicator display window will change to red, as shown in the shaded area, when there are only 20 puffs of medicine left in your inhaler (**See Figure 2d).**

Preparing your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler for use:

- Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) should be at room temperature before you use it.
- Your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler comes in a foil pouch that contains a drying packet (desiccant).
  - Take the Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler out of the foil pouch.
  - Throw away the pouch and the drying packet. Do not eat or breathe in the contents of the drying packet.

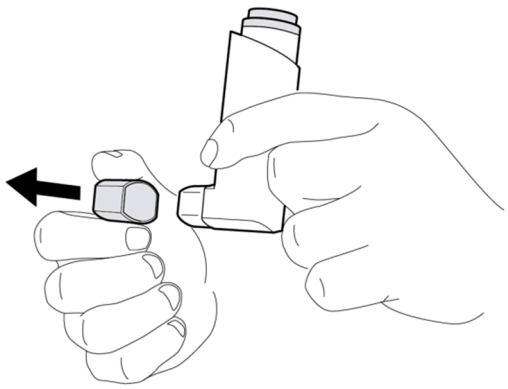

Figure 3

Priming your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler:

Before you use Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) for the first time, you must prime the inhaler.

- Remove the cap from the mouthpiece (**See Figure 3**). Check inside the mouthpiece for objects before use.
- Hold the inhaler in the upright position away from your face and shake the inhaler well (**See Figure 4**).

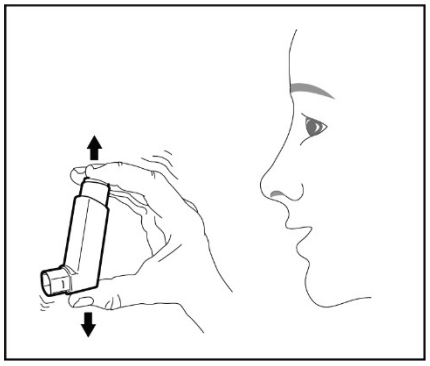

Figure 4

- Press down firmly on the centre of the dose indicator until the canister stops moving in the actuator**,** to release a puff of medicine from the mouthpiece (**See Figure 5**). You may hear a soft click from the dose indicator as it counts down during use.

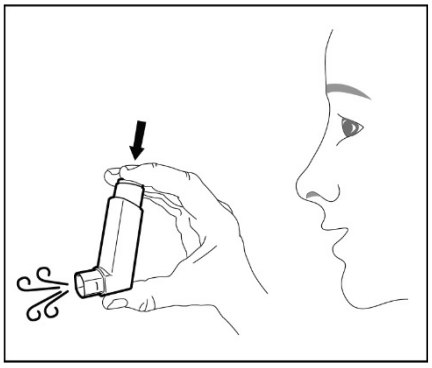

Figure 5

- **Repeat the priming steps 3 more times (See Figure 4 and Figure 5).** Shake the inhaler well before each priming puff.
- After priming 4 times, the dose indicator should be pointing to the right of "**120**" and your inhaler is now ready to use.

Using your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler:

Step 1: Remove the cap from the mouthpiece (**See Figure 6**).

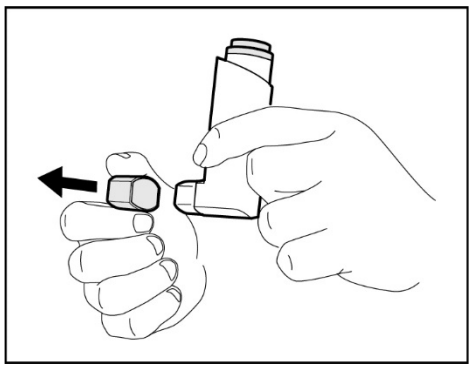

Figure 6

Step 2: Shake the inhaler well before each use (**See Figure 7**).

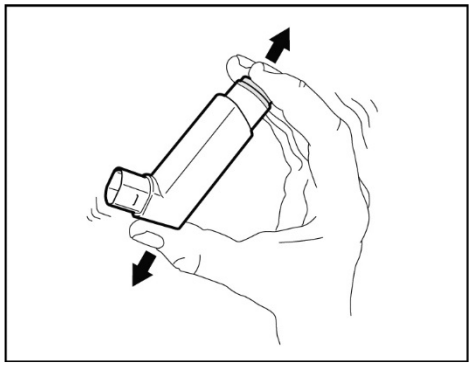

Figure 7

Step 3: Hold the inhaler with the mouthpiece pointing towards you and breathe out as fully as you comfortably can through your mouth (**See Figure 8**).

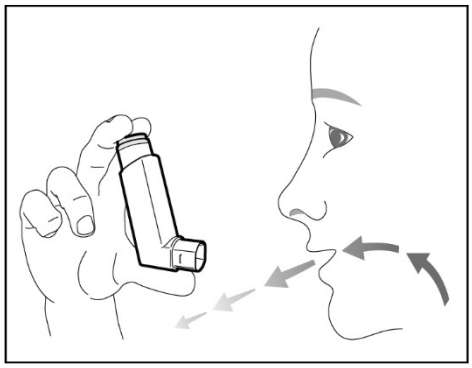

Figure 8

Step 4: Close your lips around the mouthpiece and tilt your head back, keeping your tongue below the mouthpiece (**See Figure 9**).

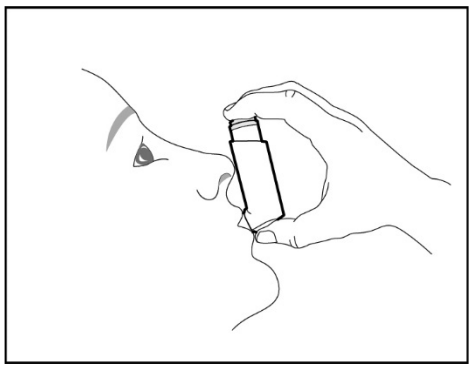

Figure 9

Step 5: While breathing in deeply and slowly, press down on the centre of the dose indicator until the canister stops moving in the actuator and a puff of medicine has been released (**See Figure 10**). Then stop pressing the dose indicator.

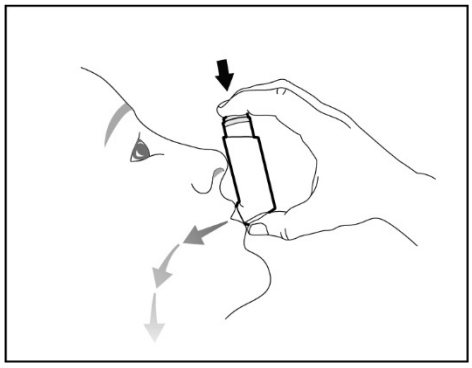

Figure 10

Step 6: When you have finished breathing in, remove the mouthpiece from your mouth. Hold your breath as long as you comfortably can, up to 10 seconds (**See Figure 11**).

Figure 11

Step 7: Breathe out gently (**See Figure 12**). **Repeat steps 2 through 7** to take your second puff of Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE).

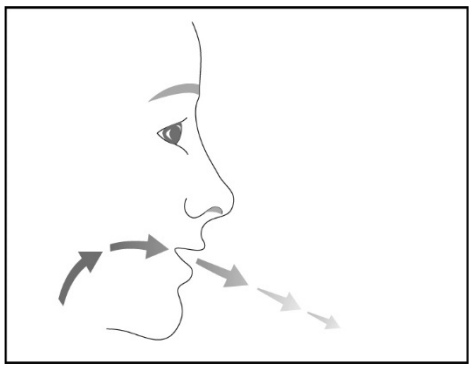

Figure 12

Step 8: Replace the cap over the mouthpiece right away after use (**See Figure 13**).

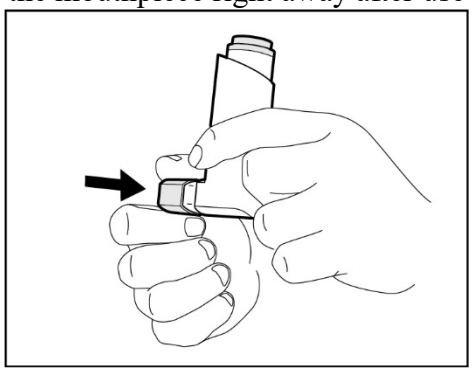

Figure 13

How to clean your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler:

Clean the inhaler 1 time each week for the first 3 weeks. It is very important to keep your inhaler clean so that medicine will not build-up and block the spray through the mouthpiece (**See Figure 14**).

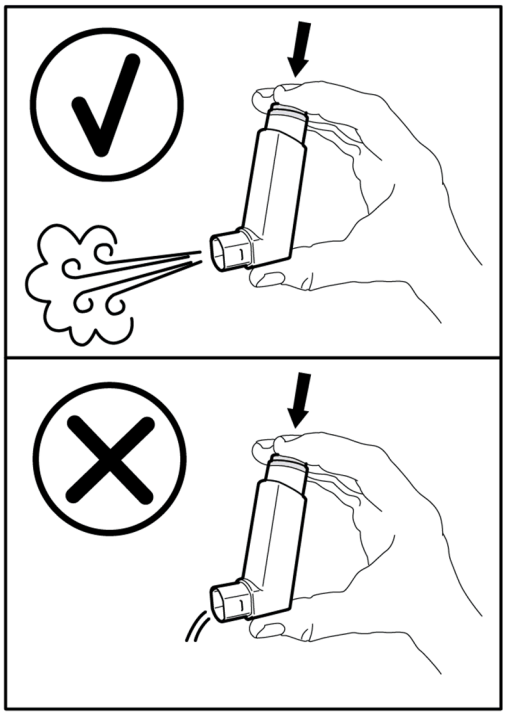

Figure 14

Step 1: Take the canister out of the actuator (**See Figure 15**). **Do not** clean the canister or let it get wet.

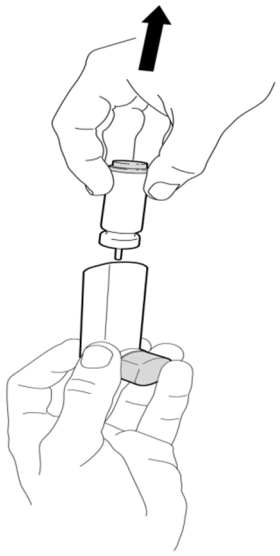

Figure 15

Step 2: Take the cap off the mouthpiece.

Step 3: Hold the actuator under the faucet and run warm water through it for about 30 seconds. Turn the actuator upside down and rinse the actuator again through the mouthpiece for about 30 seconds (**See Figure 16**).

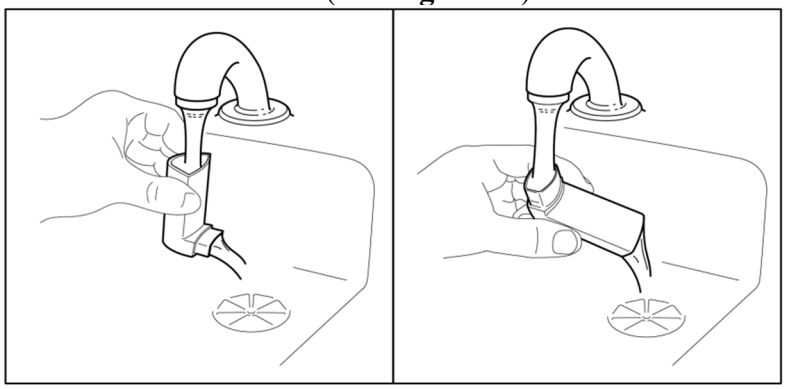

Figure 16

Step 4: Shake off as much water from the actuator as you can.

Step 5: Look into the actuator and the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Steps 3 through 5 in the section "**How to clean your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) inhaler".**

Step 6: Let the actuator air-dry overnight (**See Figure 17**). **Do not** put the canister back into the actuator if it is still wet.

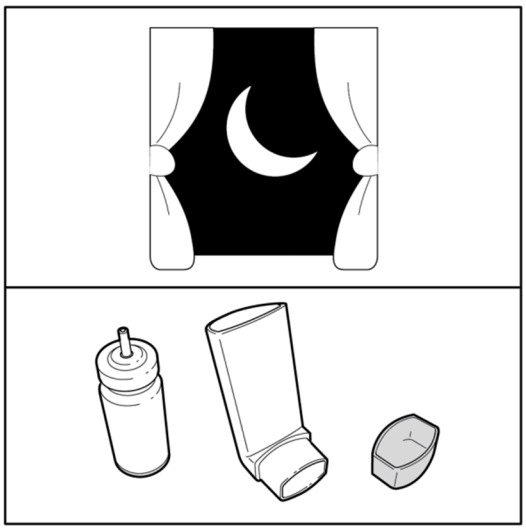

Figure 17

Step 7: When the actuator is dry, gently press the canister down in the actuator (**See Figure 18**). Do not press down too hard on the canister. This could cause a puff of medicine to be released.

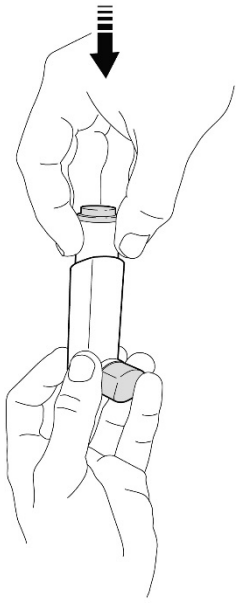

Figure 18

Step 8: Re-prime your **Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE)** inhaler after each cleaning. To re-prime the inhaler, shake the inhaler well and press down on the centre of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

If you do not use your Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) for more than 7 days, or if the inhaler is exposed to low temperatures or has been dropped, you will need to re-prime it before use.

To re-prime the inhaler, shake the inhaler well and press down on the centre of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

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REGISTRATION NUMBER
Glycopyrronium/ Formoterol fumarate dihydrate (BEVESPI AEROSPHERE) 7.2 mcg/ 5.0 mcg per actuation Pressurised Suspension for Inhalation – DR-XY_____

DATE OF FIRST AUTHORIZATION
19 November 2021

DATE OF REVISION OF PACKAGE INSERT
November 2021
Based on CDS dated 07 February 2020 with ANGEL Ref.: Doc ID-003371512 v.5.0 and CPIL dated 07 February 2020 with ANGEL Ref.: Doc ID-003104416 v.4.0
Philippine-specific Text ANGEL Reference: Doc ID-003806064 v.3.0